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(54) Title: USE OF INSULIN SENSITIZING AGENTS TO TREAT HYPERTENSION

(57) Abstract

The present invention provides a method for treating hypertension in insulin resistant patients comprising the administration of an insulin sensitizing agent, particularly ciglitazone or pioglitazone.

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USE OF INSULIN SENSITIZING AGENTS TO TREAT HYPERTENSION

BACKGROUND

The present invention provides a new use of known pharmaceutical compounds. In particular, the present invention provides for the treatment of hypertension with certain insulin sensitizing agents such as thiazolidinedione derivatives. These compounds are previously known for the treatment of diabetes.

The fact that there was a relationship between circulating insulin and hypertension has been frequently discussed in the literature. Thus, for example, Pereda, et al, Am. J. Physiol. 202 (2): 249-252 (1962) noted an increase in blood pressure in dogs due to the administration of insulin. DeFronzo, Diabetologia 21: 165-171 (1981) attributed this increase in hypertension to the effect of insulin on renal sodium retention which expanded the vascular volume, while Rowe, et al, Diabetes 30:219-225 (March 1981) attributed it to the increased activity of the sympathetic nervous system. Other studies have suggested that hyperinsulinemia as the result of insulin resistance is associated with hypertension. This is attributed to the fact that obesity is known to be associated with insulin resistance and it is a commonly held view that hyperinsulinemia in obesity is a major factor responsible for hypertension. See, e.g., Modan, et al, J. Clin. Invest. 75:809-817 (March 1985). Patients with essential hypertension have been reported to have insulin resistance. Ferrannini, et al, N. Eng. J. Med. 317:350-7 (1987). In the last study a measure of insulin resistance was reported to directly correlate with arterial blood pressure. In patients with a functional endocrine pancreas, insulin resistance also correlates directly with circulating insulin levels.

Ciglitazone is characteristic of a new class of thiazolidine antidiabetic agents which lower blood glucose in animal models of noninsulin diabetes mellitus (NIDDM), while actually reducing circulating concentrations of insulin. This is believed to be accomplished by improving the responsiveness of the peripheral tissues to insulin. See, e.g., Chang, et al, Diabetes 32:830-838 (September 1983).

Because of the high association between diabetes, obesity, and hypertension, and the increase in risk of heart attack in patients exhibiting both diabetes and hypertension (see, e.g., Tzagournis, Am. J. Med., 86 (suppl 1B):50-54 (1989)), what is needed in the art is an agent which will treat both diabetes and hypertension.

INFORMATION DISCLOSURE

Thiazolidine derivatives useful for the treatment of diabetes are described in U.S. patents 4,287,200; 4,687,777; and 4,572,912. Their effect on insulin resistance are described, e.g., Chang, et al, Diabetes 32: 839-845 (1983) and Chang, et al, Diabetes 32:830-838 (1983). The association between circulating insulin and hypertension has been discussed in the literature, as described above.

SUMMARY OF THE INVENTION

The present invention particularly provides a method for treating or preventing hypertension in an insulin-resistant patient comprising the administration of an insulin sensitizing compound to said patient in an amount effective to treat or prevent hypertension. Also provided are specific insulin sensitizing agents for use in this method including thiazolidinediones such as ciglitazone, pioglitazone, and CS 045, metformin, certain indole amines and thermogenic beta agonists.

Surprisingly and unexpectedly, the present invention provides a class of agents useful to treat insulin resistant patients; these agents have an especially good effect in the lowering of blood pressure in said patients.

By insulin sensitizing agent is meant any agent which will lower blood glucose levels by increasing the responsiveness of the tissues to insulin.

By patients susceptible to insulin resistant hypertension is meant a patient who exhibits insulin resistance and is therefore likely to exhibit hypertension. Such patients are well known and readily determinable by a physician of ordinary skill in the art.

By treatment is meant any lowering of blood pressure caused by insulin resistance and/or high circulating insulin levels. By prevention is meant partial to total avoidance of hypertension in insulin resistant patients, depending on the severity of the disease.

The thiazolidinediones are particularly useful in the present invention and are made by the methods described in U.S. patents 4,287,200; 4,687,777; and 4,572,912, which are expressly incorporated by reference herein. The dosage forms and modes of administration described therein are also useful for carrying out the method of the present invention. More specific dose ranges are set out below.

Thermogenic beta agonists are a well known class of antidiabetic agents, exemplified by, e.g., compounds BRL 26,830 (see Biochemica and Biophysica Research Comm. 128:928-935 (1985); and BRL 35,135 (Diabetes, Vol. 35: Abstract No. 262 and 263, 1986) being developed by SmithKline-Beecham. Metformin is described, e.g., in Petersen, et al., Diabetic Medicine 6:249-256 (1989). A class of diabetic indole amines

are described in copending application Serial No. 07/270,551, filed 14 November 1988, and PCT application PCT/US89/04711, filed 27 October 1989.

The preferred compounds of this invention include ciglitazone, (2,4-thiazolidinedione, 5-[[4-[(1-methylcyclohexyl)methoxy]phenyl]methyl]-, (±)- or (±)-5-[*p*-[(1-methylcyclohexyl)methoxy]benzyl]-2,4-thiazolidinedione);Pioglitazonehydrochloride(5-[[4-[2-(5-ethyl-21-pyridinyl-ethoxy]phenyl]methyl]-,monohydrochloride, (±); (2) (±)-5-[*p*-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione monohydrochloride) ; and CS 045 (5-(4-((3,4-dihydro-6-hydroxy-2,5,7,8 tetramethyl-2H-1-benzopyran-2-yl)methoxy)phenyl)methyl)-2,4-thiazolidinedione).

While any convenient route of administration is employed, the preferred thiazolidinedione compounds of the present invention are preferably orally administered to humans to affect insulin sensitization for the purpose of favorably affecting blood pressure. For this purpose, the compounds are administered from 100 micrograms per kg to 6 mg per kg per dose, administered from 1 to 3 times daily. Other routes of administration, such as parenteral (including intravenous, intramuscular, and intraperitoneal) are also employed. Equipotent doses for the other compounds of this invention and the other routes of administration would thus be employed, and could be readily determined by a physician of ordinary skill.

The exact dose depends on the age, weight, and condition of the patient and the frequency and route of administration. Such variations are within the skill of the practitioner or can readily be determined.

The employment of sound medical therapy requires that the compounds of this invention be employed prophylactically only in cases where the animal or patient is particularly susceptible to the development of hypertension. The conditions and circumstances which increase the susceptibility are readily ascertainable to the ordinary skilled physician and include glucose intolerance, insulin resistance, hyperinsulinemia and obesity.

In the prophylactic use of these compounds, the dose effective for the prevention of hypertension is readily determined by patient response, as discussed above for therapeutic uses, and is, in general, somewhat less than the dose required to treat the disease.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is seen more fully by the Example given below.

Example 1

Ciglitazone was tested in the Zucker rat, a well known model of insulin resistant mammals and was shown to lower blood pressure, as described below:

Two groups of 6-week old obese female Zucker (fa/fa) rats, 10 control and 10 experimental, were fed a diet containing: 65% carbohydrate, 18% protein, 5% fat, 5% fiber, 0.1% sodium chloride (NaCl), with the remainder containing water, vitamins and minerals.

The experimental group received the drug (ciglitazone powder) as a 0.05% (w/w) dietary admixture (33 to 58 mg/kg body weight/day, calculated from food intake) for 30 days. The control group did not receive the drug.

The mean arterial pressure (MAP) was measured in the unanesthetized, unrestrained state by indwelling femoral artery catheters attached to a pressure transducer, and blood drawn for measurement of blood glucose and plasma insulin concentrations. The results of the study are set forth in Table 1.

Example 2

The effect of insulin sensitizing compounds in primates was shown as follows. Obese, insulin-resistant Rhesus monkeys were given pioglitazone (1 mg/kg/day, oral gavage) for two weeks. Glucose tolerance was substantially improved in 5 of 6 monkeys. Systolic blood pressure was reduced an average of 16 mmH; mean arterial blood pressure (MAP) was reduced an average of 8.4 mmHg. These data show that improved insulin sensitivity produced by drugs of this type are an effective treatment for lowering blood pressure.

TABLE 1

Effects of Ciglitazone on Mean Arterial Pressure (MAP) and Urine Output

Measurement	Control	Ciglitazone	Significance[1]
MAP (mm Hg)	119 ± 2 (n=9)	112 ± 4 (n=6)	$p < 0.05$[2]
Urine Output	80 ± 5 (n=9)	97 ± 8 (n=6)	$p < 0.05$[3]
Insulin (mU/ml)	171 ± 20	60 ± 9	

There was no significant difference in body weight or food intake between both groups over the period of the experiment. Because of complications during surgery, one animal was lost from the control group, and 4 from the experimental group.

Ciglitazone significantly lowered blood pressure in the fa/fa Zucker rats.

1. The data is presented as the mean ± SEM and significance determined with the paired Students' t-test.

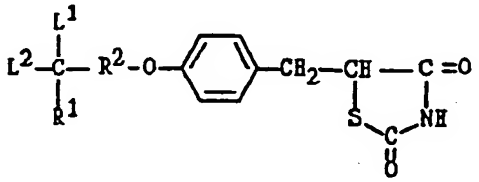
2. The one-tailed t-test was used to compare blood pressure measurements.

3. The two-tailed t-test was used to compare urine output measurements.

CLAIMS

1. Use of an insulin sensitizing compound to prepare a medicament for treating or preventing hypertension in an insulin-resistant patient.

2. A use of Claim 1 wherein the compound is a thiazolidinedione derivative of the general Formula I



wherein R^1 is alkyl of 1 to 10 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenyl alkyl of 7 to 11 carbon atoms, or phenyl;

wherein R^2 means a bond or a lower alkylene group; wherein L^1 and L^2 are the same or different and each is lower alkyl or L^1 and L^2 are combined to form an alkylene group, provided that when R^1 is other than alkyl, L^1 and L^2 may further be hydrogen.

3. A use of Claim 2, wherein the compound is ciglitazone.

4. A use of Claim 1, wherein the compound is pioglitazone hydrochloride.

5. A use of Claim 1, wherein the compound is metformin.

6. A use of Claim 1, wherein the compound is an antidiabetic indole amine.

7. A use of Claim 1, wherein the compound is a thermogenic ß-agonist.

8. A use of Claim 1, wherein the compound is CS 045.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/00348

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 31/425,A 61 K 31/44,A 61 K 31/155,A 61 K 31/40, A 61 K 31/235,A 61 K 31/135,A 61 K 31/35

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
IPC[5]	A 61 K 31/00,C 07 D 277/00,C 07 D 417/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
P,X	EP, A2, 0 356 214. (BEECHAM GROUP PLC) 28 February 1990 (28.02.90), see abstract, claims 14-17, page 1, line 3 - page 4, line 12, especially page 1, lines 10-61.	1
Y	EP, A1, 0 006 735 (BEECHAM GROUP LIMITED) 09 January 1980 (09.01.80), see abstract, page 1, line 7 - page 9, line 22, claims 22 -25.	1,7
Y	The New England Journal of Medicine, vol. 317, published 1987, Melbourne E. Ferrannini et al. "Insulin Resistance in Essential Hypertension", see pages 350-357, especially page 350,	1,7

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
23 April 1991	23 MAY 1991
International Searching Authority	Signature of Authorized Officer
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Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
	abstract and left column, line 1 - right column, line 2, pages 354-356, discussion (cited in the application). --	
Y	Biochemical and Biophysical Research Communications, vol. 128, published 1985, San Diego, Orlando, New York, London, Toronto, Montreal, Sydney, Tokyo, R.A.J. Challiss et al. "Effect of a Novel Thermogenic beta-adrenoceptor agoinst (Brl 26830) on Insulin Reistance in Soleus Muscle from Obese Zucker Rats", see pages 928-935, especially page 928, summary, page 929, results (cited in the application). --	1,7
Y	EP, A2, 0 283 369 (LIPHA) 21 September 1988 (21.09.88), see claims 1,3-8, page 2, lines 18-34. --	1,5
Y	Diabetic Medicine, vol. 6, published 1989, O. Pedersen et al. "The Effects of Metformin on Adipocyte Insulin Action and Metabolic Control in Obese Subjects with Type 2 Diabetes", see pages 249-256, especially page 249, abstract and left column (cited in the application). --	1,5
A	Diabetes, vol. 35, supplement 1, published 1986, Anaheim, Us, page 66 A, M.V. Sennitt et al. "Anti-hyperglycaemic activity in rats and mice of BRL 35135, a novel beta-adrenoceptor agoinst", abstract no. 262, and M.A. Cawthorne et al. "Effects of BRL 35135, a novel type of beta-adrenoceptor agoinst, on glucose tolerance and insulin sensitivity in obese Zucker rats", abstract no.	1,7

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET) PCT/US 91/00348

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
	263 (cited in the application). --	
A	US, A, 4 382 958 (D.M. DUCKWORTH) 10 May 1983 (10.05.83), see abstract, claims 5,6. --	1,7
A	EP, A1, 0 193 256 (TAKEDA CHEMICAL INDUSTRIES LTD.) 03 September 1986 (03.09.86), see abstract, claims 5,6, page 1, line 17 - page 2, line 23, page 3, line 22 - page 4, line 1, example 2. --	1,4
A	EP, A1, 0 008 203 (TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA) 20 February 1980 (20.02.80), see abstract, claims 7,8, example 13, page 4, lines 6-26, example 9, compounds no. 40-49. --	1-4
A	Diabetes, vol. 32, published 1983, A.Y. Chang et al. "Ciglitazone, a New Hypoglycemic Agent II", see pages 835-845, especially page 839, summary, page 845, last paragraph (cited in the application). --	1,3
A	US, A, 4 572 912 (T. YOSHIOKA et al.) 25 February 1986 (25.02.86), see abstract, column 1, line 21 - column 2, line 53, claims 24-37 (cited in the application). --	1,8
A	US, A, 3 542 927 (J.M. McMANUS et al.) 24 November 1970 (24.11.70), see claims 1-6, abstract, column 3, line 43 - column 4, line 74, examples XII, XIII. --	1,6
A	EP, A2, 0 166 183 (MERCK PATENT GESELLSCHAFT	1,6

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
	MIT BESCHRÄNKTER HAFTUNG) 02 January 1986 (02.01.86), see abstract, claim. --	
A	The Journal of Clinical Investigation, vol. 75, published 1985, M. Modan et al. "Hyperinsulinemia", see pages 809-817, especially page 809, abstract (cited in the application). ----	1

ANHANG
zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX
to the International Search Report to the International Patent Application No.

ANNEXE
au rapport de recherche international relatif á la demande de brevet international n°

PCT/US91/00348 SAE 44313

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Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP-A2- 356214	28-02-90	EP-A3- 356214	08-08-90
		GB-A0- 8820389	28-09-88
		JP-A2- 2083384	23-03-90
EP-A1- 6735	09-01-80	AU-A1-48498/79	03-01-80
		AU-B2- 523681	12-08-82
		CA-A1- 1159072	20-12-83
		DE-C0- 2965655	21-07-83
		DK-A - 2727/79	04-02-80
		EP-B1- 6735	15-06-83
		ES-A1- 483746	16-04-80
		ES-A5- 483746	16-05-80
		IE-B - 48580	06-03-85
		IL-A0- 57678	31-10-79
		JP-A2-55009085	22-01-80
		JP-B4- 1030820	22-06-89
		MY-A - 958/85	31-12-85
		MY-A - 959/85	31-12-85
		US-A - 4478849	23-10-84
		US-A - 4654371	31-03-87
		US-A - 4753962	28-06-88
		NZ-A - 190854	19-10-84
		ZA-A - 7903231	30-07-80
		ES-A3- 546425	01-02-86
		ES-A3- 8604483	01-07-86
		ES-A7- 546425	26-02-86
EP-A2- 283369	21-09-88	AU-A1-12727/88	08-09-88
		DK-A0- 1167/88	04-03-88
		DK-A - 1167/88	07-09-88
		EP-A3- 283369	29-11-89
		FR-A1- 2611500	09-09-88
		FR-B1- 2611500	04-05-90
		IL-A0- 85627	31-08-88
		JP-A2-63230628	27-09-88
		ZA-A - 8801540	26-10-88

US-A - 4382958	10-05-83	AU-A1-77624/81	27-05-82
		AU-B2- 546377	29-08-85
		CA-A1- 1175444	02-10-84
		DE-C0- 3169094	28-03-85
		EP-A1- 52963	02-06-82
		EP-B1- 52963	20-02-85
		ES-A1- 507298	16-02-83
		ES-A5- 507298	14-03-83
		ES-A1- 8304063	16-05-83
		ES-A1- 516472	01-11-83
		ES-A5- 516472	30-11-83
		ES-A1- 8400390	16-01-84
		GB-A1- 2096988	27-10-82
		GB-B2- 2096988	01-08-84
		IE-B - 52403	14-10-87
		JP-A2-57116030	19-07-82
		NZ-A - 198884	31-07-85
		PT-A - 73997	01-12-81
		PT-B - 73997	31-03-83
		ZA-A - 8107881	27-10-82
EP-A1- 193256	03-09-86	AT-E - 41931	15-04-89
		AU-A1-52467/86	24-07-86
		AU-B2- 572719	12-05-88
		CA-A1- 1277323	04-12-90
		CN-A -86100411	16-07-86
		DE-C0- 3662689	11-05-89
		DK-A0- 219/86	17-01-86
		DK-A - 219/86	20-07-86
		EP-B1- 193256	05-04-89
		ES-A1- 550986	16-05-87
		ES-A5- 550986	15-06-87
		ES-A1- 8705886	01-08-87
		FI-A0- 860232	17-01-86
		FI-A - 860232	20-07-86
		FI-B - 81098	31-05-90
		FI-C - 81098	10-09-90
		HU-A2- 41775	28-05-87
		HU-B - 196795	30-01-89
		NO-A - 860141	21-07-86
		NO-B - 163857	23-04-90
		NO-C - 163857	01-08-90
		PT-A - 81859	01-02-86
		PT-B - 81859	20-11-87
		US-A - 4687777	18-08-87
		ZA-A - 8600203	30-09-87
		JP-A2-61267580	27-11-86
		CN-B - 1003934	19-04-89
		AU-B2- 569365	28-01-88
		CN-B - 1003934	19-04-89
		DK-A0- 289/85	22-01-85
		DK-A - 289/85	24-07-85
		EP-A2- 150067	31-07-85
		EP-A3- 150067	30-12-86
		IL-A0- 74093	30-04-85
		JP-A2-61161222	21-07-86
		NZ-A - 210897	29-04-88
		PH-A - 22531	17-10-88
		PT-B - 79854	15-12-86
		US-A - 4714611	22-12-87
		AU-A1-38016/85	01-08-85
		AU-B2- 569365	28-01-88
		DK-A0- 289/85	22-01-85
		DK-A - 289/85	24-07-85

		EP-A3- 150067	30-12-86
		ES-A1- 539737	01-08-86
		ES-A5- 539737	01-09-86
		ES-A1- 8609367	16-12-86
		JP-A2-60155136	15-08-85
		NZ-A - 210897	29-04-88
		PH-A - 22531	17-10-88
		PT-A - 79854	01-02-85
		PT-B - 79854	15-12-86
		US-A - 4714611	22-12-87
		ZA-A - 8500497	24-09-86
		US-A - 4986984	22-01-91
		AU-A1-38017/85	01-08-85
		CA-A1- 1255220	06-06-89
		DK-A0- 288/85	22-01-85
		DK-A - 288/85	24-07-85
		EP-A2- 150066	31-07-85
		EP-A3- 150066	17-09-86
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		ES-A5- 539736	02-02-87
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		IL-A0- 74094	30-04-85
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		PT-B - 79853	15-12-86
		ZA-A - 8500496	24-09-86
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		CA-A1- 1255220	06-06-89
		CN-A -85101554	09-07-86
		DK-A0- 288/85	22-01-85
		DK-A - 288/85	24-07-85
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		EP-A3- 150066	17-09-86
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		ES-A5- 539736	02-02-87
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		ES-A5- 535552	16-06-86
		ES-A1- 8607297	01-11-86
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		FI-C - 80693	10-07-90
		JP-A2-60051189	22-03-85
		JP-B4- 2031079	11-07-90
		KR-B1- 8900370	14-03-89

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		ZA-A - 8504018	29-01-86
		US-A - 4914114	03-04-90
		AT-E - 54444	15-07-90
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		AU-B2- 594512	08-03-90
		DE-C0- 3763661	16-08-90
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		WO-A1- 8801998	24-03-88